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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
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ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/10/2002 17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/613,887	HOGAN, KIRK	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed February 8, 2002. Currently, claims 21-41 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action contains new grounds of rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 21, 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Posey J. of National Med. Association. Vol 81, No. 7, pages 793-796, July 1989) and Boral (Am. J. of Clinical Pathology, Vol 71, No. 5, pages 578-587, May 1979).

This rejection is broadly applied to the claims drawn to "genetic variations". Genetic markers has been interpreted in light of the specification, to be interpreted as a point (e.g., on a chromosome, on a viral nucleic acid or on a mitochondrial nucleic acid) for which a change (e.g. a mutation or a polymorphism) causes a genotypic or phenotypic change (page 24). This definition is not limited to detecting nucleic acids, but rather encompasses any change which causes a genotypic or phenotypic change.

The claims do not recite that obtaining a sample of nucleic acids or that nucleic acids are specifically tested for point mutations.

Posey teaches typing blood for ABO and Rh status to determine the genetic variation within the cells perioperatively, i.e. before transfusion. Posey teaches testing the blodd before used in a transfusion (i.e. perioperative testing), such that identification of homologous blood transfusion can minimize the risks and hazards of blood transfusion (abstract). Posey teaches that in the preoperative period, elective surgical candidates may predeposit autologous blood or select directed donors. Posey teaches numerous complications which may arise from transfusion which includes reactions involving the ABO system, renal failure, intravascular coagulation and death. Posey teaches that these reactions are almost always due to an error involving ABO incompatibility. Posey teaches that based upon the result of the perioperative test, i.e. that the blood is homologous, the blood is then used during the operation.

Boral et al. (herein referred to as Boral) teaches type and antibody screen for blood in medical facilities that have a moderate reserve of blood readily available for transfusion (abstract). Boral teaches that the type and antibody screen consists of an ABO-Rh typing. Boral teaches that patient's serum is tested for incompatibility against donor cells. The crossmatch between the patient's and donor's cells takes about an hour to perform. Boral teaches that identification of an antibody during the screen requires at least two units of blood, negative for the corresponding antigen to be crossmatched for that patient. Boral also teaches that "the surgeon is notified of the presence of an unexpected antibody". Therefore, Boral teaches that the type and

antibody screen is a rapid assay which allows the genetic variations within blood to be assessed to allow for a safe transfusion.

Therefore, since Posey and Boral teach typing blood for ABO and Rh status, Posey and Boral teach analyzing the blood sample prior to operation, prior to transfusion for genetic variations to avoid risks of surgery. Blood types include AO, AA, AB, BO, BB, OO. Rh status includes positive and negative. These types vary depending on the genetics of an individuals parents, such that they are genetic variations.

5. Claims 21, 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Bidwell (Technique, Vol. 2, No.2, pages 93-100, 1990).

Bidwell et al. (herein referred to as Bidwell) teaches a metod for rapidly allotype matching based upon PCR for human HLA-DR/Dw allotype. Bidwell teaches that HLA-DR and DQ matching is now generally undertaken as a clinical prerequisite for renal and bone marrow transplantation. Bidwell teaches that many polymorphisms at the DNA level exist which allow DNA typing to become more widely used as an adjunct or alternative to serological tests (page 94, col 1). Bidwell teaches that the HLA-DR/Dw allotype method is useful for matching donor and patient in the selection of living related or unrelated volunteer donors for bone marrow transplantation (page 98, col 2).

The patient which is to receive the transplantation would have been analyzed for their HLA-DR/Dw allotype following being identified for surgery and scheduled for surgery i.e. erioperatively. While the exact date for surgery may be dependent upon

finding a suitable match, the patient was scheduled for a surgical procedure as required by the instant claims. Unless, the patient had been identified for surgery, the test would have been needless and the matching of allotypings would be unneeded.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 21-28, 31-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994).

Miller teaches screening a patient preoperatively to determine a risk for complications during a surgical procedure. Miller teaches that patients meets with the surgeon to prepare for surgery. Miller teaches that the surgeon often informs the patient of the anesthetic preoperative requirements and presents the patient with a letter. A sample letter is provided which illustrates the date of the surgery with the time, and instructions that "it is also important that your blood tests, urinalysis, and any other tests ordered by your doctor be completed two days before you are scheduled for surgery so that they can be reviewed by your anesthesiologist prior to surgery". Miller therefore teaches the importance of a blood test prior to surgery to identify any abnormalities.

Miller does not specifically teach analyzing the blood taken from the patient within two days prior to surgery for "known genetic variations".

However, Quane et al (herein referred to as Quane) teaches the detection of novel common mutations in ryanodine receptor gene (RYR1) in malignant hyperthermia (MH). Malignant hyperthermia (MH) is triggered in susceptible people by all commonly used inhalation anesthetics. Quane has identified Gly341Arg mutation which accounts for approximately 10% of Caucasian MHS cases (abstract). Quane specifically teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided. Quane also teaches that Arg615Cys is a substitution found in 3-5% of human MH families investigated (page 472, col. 1); Arg163Cys is a substitution found in 2-3% of MHS cases. Furthermore, three other rare mutations have been reported in the RYR1 gene which are in three isolated MHS and/or CCD cases. Quane teaches that patients which have not been indicated as MH normal should always be considered MHS clinically to avoid any possibility of the individual reacting to a triggering agent during anesthesia. Misdiagnosis of MHS individual as MHN can be lethal if such a patient is exposed to triggering agents (page 474, col. 1). Quane teaches that the mutation reported satisfies the genetic criteria necessary for demonstration of a causal mutation and as such this mutation should be of significant value for MHS diagnosis by genetic means (page 474, col. 1). Quane analyzes genomic DNA from peripheral blood for the presence of the mutations (page 474, col 2).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients prior to subjecting the

patient to anesthetics, as taught by Miller, to determine whether they were at risk of MH, as taught by Quane. Miller teaches that it is routine to sample patients blood to analyze the blood for abnormalities including hematocrit levels. Miller teaches that "the laboratory evaluation should be available for review by the anesthesiologist prior to or at the time he first sees the patients preoperatively so that any questions regarding the pateient's status should be resolved then and if not resolved the surgery should be delayed" (page 1325). Quane provides three examples of common mutations within the RYR1 gene which are associated with MH and which trigger MH syndrome during anesthesia, and potentially death. Quane specifically states that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided" (page 471, col. 2). Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within the RYR1 gene for the expected benefit of determining whether the patient possessed any mutations which were linked to the known condition of MH to avoid any fatal reaction to the anesthesia. The ordinary artisan would have recognized that blood samples are routinely taken within two days prior to surgery and therefore to minimize inconvenience to the patient, the blood sample taken would also be an ideal sample for testing the patient for genetic abnormalities within RYR1. The ordinary artisan would have clearly recognized the benefit of testing an individual prior to surgery and subjection to the anesthesia for known genetic markers associated with a condition which was triggered by anesthetics.

Response to Arguments/Declaration

The Declaraiont is not directly relevant to the new grounds of rejection but the points regarding Quane have been addressed below. Applicant's traverse the previous grounds of rejection. The arguments have been addressed to the extent that the arguments are applicable to the newly added rejections.

The response agues that the references fail to teach that samples are tested in the perioperative period defined by the claim. This argument has been addressed by addition of Miller who teaches sampling individuals within two days prior to surgery for blood analysis.

The response argues that Quane does not suggest that medical practitioners would be motivated to test people in order to determine genetic risk for surgical complications. This argument has been thoroughly reviewed, but found unpersusavie because Quane explicitly teaches that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided." This statement provides motivation to the ordinary artisan to sample prior to treatment with anesthetics which trigger MH.

Moreover, the response argues that Quane does not teach two or more conditions. This argument has been thoroughly reviewed but found unpersuasive because Claim 37 was rejected upon a combination of references and not Quane alone. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are

based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument based upon the age of the references, contentions that the references are old are not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977).

The declaration by the invention filed under 1.132 has been thoroughly reviewed.

The response argues that the state of the art in the medical practices is to not test subjects in the perioperative period. The response continues to explain that applicant applied for a grant entitled "Perioperative Genomic Profiles" to the Anesthesia Patient Safety Foundation (APSF) and was rejected by a panel of experts because "the state of the art teaches that such methods should not be carried out". Based upon the committees excerpt, the committed states that "the committee's concern and reason for not funding the study rested on a few factors. It is a basic science study without clear clinical value. In the values equation the committee members considered the study might improve the quality but the cost could be very high". While applicants are arguing that the art is not routinely doing perioperative analysis, this is not the standard for obviousness. As provided by the statute of 103,

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

The statute does not provide that cost is a factor in considering non-obviousness. The committee does not appear to be establishing that given the art at the time of filing, that the invention was non-obvious, but the committee rather appears to be indicating that they do not think that the idea is a cost effective study. The committee has states that "as anesthesia practice has moved toward determining the ratio or quality to cost, this study seems to be going in the opposite direction". This statement is directed to the economical benefits of sampling individuals prior to surgery not the obviousness of studying individuals prior to surgery. Furthermore, the factors considered when determining whether to fund a particular study are completely different than the factors considered to determine that an invention is legally patentable. Grants are often funded because they offer an immediate use, return on value or information that the community may build upon. These are not the criteria which must be met to obtain a patent or to show non-obviousness of the prior art references.

The response provides three references directed to the proposition that routine perioperative testing is unnecessary. First, Gregroy teaches that value of routine preoperative screening tests for healthy infants and children has been questioned. Gregory teaches that "routine preoperative hemoglobin or hematocrit determinations have been recommended in the past, and have been or still are required by law in some jurisdictions. However, there are a few data to support the practice of subjecting every healthy child to a painful fingerprick or venipuncture." (page 184, col 1). While this passage illustrates that individuals may be questioning the need for blood tests prior to surgery many clinicians continue to sample blood and others are required to by law.

Therefore, public policy deems it important to perform preoperative blood analysis. Similarly, Kirby teaches that routine laboratory screening tests are not cost-effective and are often inefficient. While routine screening has not yet reached the point of being cost effective and highly efficient, the cited art still provides suggestion that with regard to the RYR1, BchE, prothrombin, etc. genes, testing prior to surgery would be certainly advantageous since mortality and complications may be avoided. While it is clear that many in the medical field do not believe that routine genetic testing provides sufficient valuable information to warrant its cost, this does not imply that the art has not conceived of or thought about the perioperative genetic testing.

The response cites Hopkins to support, "the complexity of the molecular genetics of MH precludes DNA-based diagnosis at present. Thus, a modern analysis of the molecular genetics of MH concludes that DNA-based testing for MH is precluded and not desirable". The claims are drawn to detecting two or more genetic markers to generate a genomic profile useful in selecting perioperative course of action. The claims are not drawn to diagnosing MH. Furthermore, the reference of Hopkins provides as much enabling disclosure as the instant application.

7. Claims 21, 26-28, 31-34, are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991).

Miller teaches screening a patient preoperatively to determine a risk for complications during a surgical procedure. Miller teaches that patients meets with the surgeon to prepare for surgery. Miller teaches that the surgeon often informs the patient of the anesthetic preoperative requirements and presents the patient with a letter. A sample letter is provided which illustrates the date of the surgery with the time, and instructions that "it is also important that your blood tests, urinalysis, and any other tests ordered by your doctor be completed two days before you are scheduled for surgery so that they can be reviewed by your anesthesiologist prior to surgery". Miller therefore teaches the importance of a blood test prior to surgery to identify any abnormalities.

Miller does not specifically teach analyzing the blood taken from the patient within two days prior to surgery for "known genetic variations".

However, Acta Anaesthesiologica Scandinavin (referred to as AAS) teaches that certain variants have a dramatic degree of resistance to the drug, succinylcholine (SC), because they destroy it so rapidly. AAS teaches that individuals show no regular metabolic disorder unless SC or mivacurium is given such that the condition is provoked. BchE mutations are dibucaine resistant, fluoride resistant or silent.

La Du et al (herein referred to as La Du) teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine. Variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients within two days prior to surgery, as taught by Miller, to subjecting the patient to succinylcholine, for example, to determine whether they were resistant to the drug, as taught by AAS and La Du . Miller teaches that "the laboratory evaluation should be available for review by the anesthesiologist prior to or at the time he first sees the patients preoperatively so that any questions regarding the patient's status should be resolved then and if not resolved the surgery should be delayed" (page 1325). The ordinary artisan would have clearly recognized the benefit of testing an individual within two days prior to surgery and subjection to succinylcholine for known genetic markers associated with a condition which causes certain individuals to have a dramatic degree of resistance to the drug because they destroy it so rapidly requiring two or three doses to achieve the desired state of paralysis. The ordinary artisan would have recognized that blood samples are routinely taken within two days prior to surgery and therefore to minimize inconvenience to the patient, the blood sample taken would also be an ideal sample for testing the patient for the numerous genetic abnormalities within BchE. The ordinary artisan would have been motivated to test these individuals prior to surgery for the expected benefit of determining whether the patient possessed any mutations which were linked to the known condition of rapid metabolizers to avoid ineffective treatment.

8. Claims 21, 26-28, 31-34, are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of

Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999).

Miller teaches screening a patient preoperatively to determine a risk for complications during a surgical procedure. Miller teaches that patients meets with the surgeon to prepare for surgery. Miller teaches that the surgeon often informs the patient of the anesthetic preoperative requirements and presents the patient with a letter. A sample letter is provided which illustrates the date of the surgery with the time, and instructions that "it is also important that your blood tests, urinalysis, and any other tests ordered by your doctor be completed two days before you are scheduled for surgery so that they can be reviewed by your anesthesiologist prior to surgery". Miller therefore teaches the importance of a blood test prior to surgery to identify any abnormalities.

Miller does not specifically teach analyzing the blood taken from the patient within two days prior to surgery for "known genetic variations".

However, Pharmacogenetics teaches polymorphisms of desbrisoquine hydroxylase (Cytochrome P4502D6). The structures of CYP2D gene clusters are provided. The poor metabolizers are depicted. Pharmacogenetics teaches that for drugs such as codeine and encainide it is the PM subjects who may experience therapeutic failure (page 317, col. 1). Codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. The discovery and identification of each of these conditions has saved some lives and may prevent future fatalities or morbidities.

Evans et al (herein referred to as Evans) teaches the drug-metabolizing enzyme debrisoquine hydroxylase (CYP2D6) is polymorphic. Evans teaches that "inherited differences in drug-metabolizing capacity are generally monogenic traits and their influence on the pharmacokinetices and pharmacologic effects of medications is determined by their importance for the activation or inactiviation of drug substrates (page 487, col. 2). Evens also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymoprhic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Evans illustrates in Figure 2, drug-metabolizing enzymes known to exhibit genetic polymorphisms with incontrovertible clinical consequences. Further, severe and potentially fatal hematopoietic toxicity that occurs when thiopurine methyltransferase-deficient patients are treated with standard doses of azathioprine or mercaptopurine. Evans teaches that "many opioid analgesics are activated by CYP2D6 rendering the 2-10% of the population who are homozygous for nonfunctional CYP2D6 mutant alleles relatively resistant to opioid analgesic effects. Thus is it not surprising that there is remarkable interindividual variability in the adequacy of pain relief when uniform doses of codeine are widely prescribed" (page 489, col. 1). Evans teaches that individualizing drug dosages can improve clinical outcome (page 491, col. 1).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients within two days prior to

surgery, as taught by Miller, to subjecting the patient to anesthetics to determine whether they were at risk of being a poor metabolizer of a drug, namely codeine. Miller teaches that "the laboratory evaluation should be available for review by the anesthesiologist prior to or at the time he first sees the patients preoperatively so that any questions regarding the patient's status should be resolved then and if not resolved the surgery should be delayed" (page 1325). The ordinary artisan would have clearly recognized the benefit of testing an individual within two days prior to surgery and subjection to codeine for known genetic markers associated with a condition which causes certain individuals to be poor metabolizers. The ordinary artisan would have recognized that blood samples are routinely taken within two days prior to surgery and therefore to minimize inconvenience to the patient, the blood sample taken would also be an ideal sample for testing the patient for the numerous genetic abnormalities within CYP2D6. The ordinary artisan would have been motivated to test these individuals prior to surgery for the expected benefit of determining whether the patient possessed any mutations which were linked to the known condition of poor metabolizers to avoid ineffective analgesia or therapeutic failure.

9. Claims 21, 28, 30-32, 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Poort et al (Blood, Vol 88, No. 10, page 3698-3703, 1996).

Miller teaches screening a patient preoperatively to determine a risk for complications during a surgical procedure. Miller teaches that patients meets with the

surgeon to prepare for surgery. Miller teaches that the surgeon often informs the patient of the anesthetic preoperative requirements and presents the patient with a letter. A sample letter is provided which illustrates the date of the surgery with the time, and instructions that "it is also important that your blood tests, urinalysis, and any other tests ordered by your doctor be completed two days before you are scheduled for surgery so that they can be reviewed by your anesthesiologist prior to surgery". Miller therefore teaches the importance of a blood test prior to surgery to identify any abnormalities.

Miller does not specifically teach analyzing the blood taken from the patient within two days prior to surgery for "known genetic variations".

However, Poort et al (herein referred to as Poort) teaches an 20210 AG gentoype of the prothrombin gene which is a candidate for venous thrombosis in patients. It is well known in the art that venous thromboembolism can occur without apparent cause, after surgical procedures or trauma. Poort also teaches that factor V Leiden is the most common hereditary risk factor for thrombosis. Poort teaches two genetic markers which are associated with thrombosis.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients prior to subjecting the patient to anesthetics, as taught by Miller, to determine whether they were at risk of thrombosis, as taught by Poort. Miller teaches that it is routine to sample patients blood to analyze the blood for abnormalities including hematocrit levels. Miller teaches that "the laboratory evaluation should be available for review by the anesthesiologist prior to

or at the time he first sees the patients preoperatively so that any questions regarding the patient's status should be resolved then and if not resolved the surgery should be delayed" (page 1325). Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within the prothrombin and factor V Leiden gene for the expected benefit of determining whether the patient possessed any mutations which were linked to the known condition of thrombosis to avoid any reactions. The ordinary artisan would have recognized that blood samples are routinely taken within two days prior to surgery and therefore to minimize inconvenience to the patient, the blood sample taken would also be an ideal sample for testing the patient for genetic abnormalities within would prothrombin and factor V leiden. The ordinary artisan would have been motivated to test individuals prior to surgery for the expected benefit of determining whether the patient possessed any mutations which were linked to the known condition to avoid and be aware of potential side effects which should be part of the consideration of the patient when deciding to undergo surgery.

10. Claims 29-30, 36-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) as applied to Claims 21-28, 31-35 above; Miller (Anesthesia, Vol. 2, pages 1323-1333) Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) as applied to Claims 21,26-28, 31-34 above; Miller (Anesthesia, Vol. 2,

pages 1323-1333, 1981) in view of Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) as applied to Claims 21, 26-28, 31-34 above; and Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Poort et al (Blood, Vol 88, No. 10, page 3698-3703, 1996) as applied to Claims 21, 28, 30-32, 36 above.

None of the cited references specifically discuss testing multiple known markers which are associated with different conditions, i.e. known genetic markers into a single assay for determining whether individuals are at risk during surgical procedures.

However, the state of the art with relation to known polymorphisms and detecting the polymorphisms as indicative of certain disease which either trigger episodes when exposed to anaethetics, or are poor metabolizers or potentially cause thrombosis are well known.

The ordinary artisan would have been motivated to have screened individuals within two days prior to surgery to determine the genetic composition of the individuals to provide individualized diagnosis. Miller teaches that it is routine to sample patients blood to analyze the blood for abnormalities including hematocrit levels. Miller teaches that "the laboratory evaluation should be available for review by the anesthesiologist prior to or at the time he first sees the patients preoperatively so that any questions regarding the patient's status should be resolved then and if not resolved the surgery should be delayed" (page 1325). Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within any of the known genes for known mutations which are associated with known conditions for the

expected benefit of determining whether the patient possessed any mutations which were linked to the known conditions such that the clinician may avoid any adverse reactions to the surgical procedure. The ordinary artisan would have recognized that blood samples are routinely taken within two days prior to surgery and therefore to minimize inconvenience to the patient, the blood sample taken would also be an ideal sample for testing the patient for genetic abnormalities within would be analyzed for the mutations which are causative and trigger conditions. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the vast number of teachings, as exemplified by the extremely voluminous Information Disclosure Statement filed, to screen individuals prior to surgery for several genetic markers which are indicative of any number of conditions which are caused by anaethesia or are a result of anaethesia. The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed the anaetheseologist to determine whether plausible substitutes may be provided to patients which would not cause these conditions to arise. Specifically, detection of RYR1 polymorphisms which are associated with MH would indicate to the anaetheologist that drugs which trigger the episodes should be avoided. Moreover, codeine should be administered with care to individuals having certain BchE mutations. Combining more than one screening method to determine the genomic profile of a patient would have provided the anaetheseologist with a more complete picture of the

patients genetic make-up. As suggested in many of the articles, individual treatment and screening is ideal for analysis of the genetic make-up of patients.

Conclusion

11. No claims allowable.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Brandt et al (Human Molecular Genetics, Vol. 8, No. 11, pages 2055-2062, 1999) teaches that 21 RYR1 mutations have been identified which account for more than 50 of the families with susceptibility to MH. Brandt teaches that the genetic testing may be used to determine whether individuals are likely to have MH.

B) Ciccone et al (herein referred to as Ciccone) teaches that "In anaesthesia, our preoperative assessment includes prescribed medications and allergies to drugs. We also consider factors, either directly or indirectly, which may influence responses to drugs, such as age, genetic history, metabolic phenotype,..." (page 255-256).

C) Monnier et al (herein referred to as Monnier) teaches a novel mutation in CACLN1A3 which segregate perfectly with the MHS phenotype in a French family. The substitution of an Arg-His at residue 1086 results in the transition of A for G3333.

D) Jensen et al (Acta Anaesthesiologica Scandnavica, Vol 39, page 150-156) teaches that patients with abnormal BchE often have prolonged apnoea following succinylcholine. Jensen teaches that on should not try to treat the block, but rather keep the patient anaesthetized and ventilated till the usually clinical criteria for full

recovery are present. Further, when a clinician is faced with a patient with an apparent abnormal response to succinylcholine, the use of a nerve stimulator is urged.

E) Masterson et al (Br. J. of Anaesthesia, Vol 77, No. 5, page 569-571, 1996) teaches that patients which are likely to mount excessive cytokine responses after surgery may be tested. "Such tests may help anaesthetists to predict outcome or the need for postoperative intensive care. They may also allow us to select the most appropriate anaesthetic, in terms of its ability to modulate cytokine activity, for each patient.

F) Caplan teaches numerous costs of adverse outcomes for anesthesia-related deaths. Among these costs is not only the economic costs, but also non-economic costs.

G) Larson et al (herein referred to as Larson) teaches the preoperative testing for a T to C transition in the codon for amino acid 85 of the beta globin gene. The individual was tested for an unstable Hb variant resulting in congenital hemolytic anemia which has an increased affinity for oxygen. Larson teaches that chronic hemolysis may result in cholelithiasis requiring cholecysterctomy. Perioperative management of this congenital hemoglobinopathy by partial-echange erythrocytapheresis to prevent introperative tissue hypoxia during general anesthesia and cholecystectomy. Lason describes the "perioperative management of a patient, with the unstable, high-oxygen-affinity Hb, HbBryn Mawr, who was deemed at risk for significant tissue hypoxia during general anesthesia and surgery".

H) Hecht et al (Anesth. Analg, Vol. 84, pg. 461-464, 1997) teaches a G1583A mutation in CACNL1A3 which is associated with HypoPP. Hecht also teaches that HypoPP has been identified as a disorder that can predispose a patient to the syndrome of MH which the risk of triggering skeletal muscle contraction and rhabdomyolysis, together with earlier reports of flaccid paralysis aggravated by surgery and general anesthesia, appear to favor regional anesthesia in this population whenever feasible (abstract). Hecht also teaches that MH susceptibility associated with HypoPP and of hypokalemia elicited by regional anesthesia suggests that hybrid anesthetic techniques be avoided (pg. 462, col. 2).

I) Korte et al (Clin. Chem. Lab. Med, Vol. 36, No. 4, pg. 235-240, 1998) teaches to establish a possible "perioperative reference range" for thrombin generation prothrombin fragment F1+2 and fibrin degradation markers were measured (abstract). Korte also teaches that preoperative determination of molecular markers would be helpful in identifying a group of patients at high risk for intraoperative disorder of hemostasis by exclusion of low risk patients (abstract). As seen in Table 2 and Table 3, the results of the detection assay for the two genetic markers were observed (pg. 237).

J) Brandt et al (Hum. Mol. Genetics, Vol 8, No. 11, pg 2055-2062, 1999) teaches screening of approximately 105 MH families for mutations. Despite the extensive number of known mutations in RYR1, "interpretation must be performed with care because lack of the particular mutation segregating in the family does not exclude absence of further independent unknown mutations. Additionally, genetic screening is

not yet suitable for routine diagnostics due to the low incidence of each mutation and the vastness of the gene" (pg 2058, col 2).

K) De Stefano et al (New England J. Med, Vol 341, pg 801-806, 1999) teaches screening for two point mutations, one in F 5 Leiden and one in the prothrombin gene which are the most common causes of inherited thrombophilia. Thus, carriers of both of these mutations have an increased risk of recurrent deep venous thrombosis after a first episode and are candidates for lifelong anticoagulation.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of formal matters can be directed to the patent analyst, Chantae Dessau, whose telephone number is (703) 605-1237.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
April 3, 2002

LISA B. ARTHUR
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